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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,346	03/23/2004	Jochen Urthaler	0652.2620001/EKS/VSR	3985

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
06/09/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,346	URTHALER ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-9,11-20,23,24 and 40-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5,7-9,11-20,23,40-43 and 46-50* is/are rejected.

7)☒ Claim(s) *6, 24, 44 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 3-9, 11-20, 23, 24 and 40-48 are under examination in this application.

Applicants' arguments are sufficient to overcome the rejection under 35 USC 112, second for lacking method steps as well as the coordinate rejection under 35 USC 112, first paragraph. However, newly amended 49 does not appear to be supported by the specification as set forth below. Applicants' arguments regarding the rejection under 35 USC 102 are persuasive, however, it is not clear that the claims clearly distinguish themselves from the rejections under 35 USC 103 for reasons set forth below.

As the new rejections are necessitated by applicants' amendment, this rejection is Final.

Claim Objections

The following objections are new objections necessitated by applicants' amendment.

Claim 13 should be amended to recite in line 3, --and a tubing system fluidly connecting the T-type or the Y-type connector to the clarification reactor--. If the tubing system were connecting the lysis reactor, it is not clear where the connector system would fit into the arrangement. Furthermore the Y-type connector should have an article prior to in line 3 --a T-type or Y-type connector--.

In claim 40, step b) the recitation that "the cultivated host cells are substantially disintegrated" should be amended to recite, ----the host cells of the flowed cell suspension are substantially disintegrated-- for accurate antecedent basis. Similar amendment to claim 50 is recommended.

Claim 49 recites that "the method is operated to process more than 100 grams wet cells and yield from 0.1 g to a kilogram". this suggests that the purpose of the process is to process 100 grams of wet cells and to yield the recited amounts. However, it appears as if the claim intends --wherein the cell suspension comprises more than 100 grams of wet cells and from 0.1 g to a kilogram of the biomolecule of interest is purified form the cell suspension--.

These are new objections.

Claim 14 should be amended for clarity to recite , --the two flows are transported through the neutralization reactor-- --thereby ensuring a constant ratio of cell suspension flow volume and lysis solution flow volume--. The first amendment provides location of the event whereas the later amendment is intended to clarify when the ratios are constant.

Claim 23 recites “in addition” but it is not clear to what this is in addition. This phrase can be deleted for clarity.

Claim 40, line 2 should be amended to recite --from host cells comprising the biomolecule of interest-- for clarity. Thereafter in step a) the claim should be amended to recite, -providing a cell suspension of the host cells--.

In claim 41, the recitation that the distribution means extends to a surface of the retention layer is unclear. It is not clear from where the distribution means extends. As well the recitation that the distribution means distributes the mixture “into the clarification reactor” is unclear. It would appear as if the mixture and the distribution means are both in the clarification reactor and thus it is unclear how the distribution means would function as recited. One recommendation is that the distribution means distributes the mixture onto the retention layer.

This objection is maintained for reasons of record in the office action mailed 9/4/09 and restated below.

Claim 24 is objected to for indication that the cell suspension of step a) is obtained from a cryo-pelleted cell suspension. Claim 40 states that the cell suspension is either a fermentation broth within which the host cells were cultivated or a re-suspension of the cultivated host cells harvested form the broth. It is not clear how the first condition can be met wherein the cell suspension is obtained from a cryo-pelleted cell suspension unless the starting cells that were cultivated were obtained from the cryo-pelleted cells. If this is the case the claims should be amended to recite, --wherein the cultivated host cells were obtained from cryo-pelleted cells--. Alternatively, if this is not the case, the claims should be amended to recite --wherein harvested cells were cryo-pelleted prior to resuspension--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new rejection necessitated by applicants' amendment.

The limitation "wherein the method is operated to process more than 100 grams wet cells and yield from 0.1 g to a kilogram of the biomolecule of interest" has been added to claim 49. Applicant has indicated that support for this limitation is found in ¶ 132.

> [0132] The process of the invention is scalable for processing large amounts of polynucleotide containing cells, it may be operated on a "manufacturing scale", to typically process more than 100 grams wet cells, and yielding amounts from 0.1 g to several 100 g up to kg of the polynucleotide of interest that meet the demands for clinical trials as well as for market supply.

This passage teaches that 100 grams of wet cells can be processed to produce 0.1 to 1 kilogram of polynucleotide. However, as set forth the claim is directed to any biomolecule of interest and this includes any number of envisioned biomolecules of interest.

> [0125] The process of the invention can be used for any biomolecule of interest. For the production of proteins, it may be designed such that the specific needs of the protein of interest are met. The method of the invention is independent of the fermentation process and of the source of the protein (e.g. bacteria, yeast).

The question arises as to whether the scope of claim 49 is supported by the specification. "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." Lockwood v. American Airlines Inc., 41 USPQ2d 1961, 1966 (CAFC 1997). Therefore, the limitation is impermissible NEW MATTER.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-5, 7-9, 11-20, 23, 40-43 and 46-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al (U.S. Patent No. 6,893,879; see entire document) in view of Nochumson et al (US 20060106208; see entire document). **This rejection is maintained for reasons of record in the office action mailed 9/4/09 and restated below.**

The instant methods are directed towards methods of manufacturing a biomolecule using a system wherein lysis buffer and sample are introduced into a reactor for lysis.

Petersen et al teach a method of purification of a biomolecules from samples such as E. coli (see e.g.). The method is performed on a continuous flow automated cartridge that comprises chambers for lysis, neutralization and "extraction" or "capture" (see e.g. col 9, line 15-36; col 10, line 25-30 and col 12, line 58-65). Samples are introduced into a lysis chamber or channel which can include filling elements such as glass beads (see e.g. col 3, line 35 and col 16, line 12-25) as is lysis buffer (see claim 5). The clarification chamber uses a retention layer such as a filter or flocculation that can comprise particulate matter such as beads (see e.g. col 16, line 48-64). The cartridge includes flow controllers (see e.g. col 3, line 4-5) and utilizes pressure such as air or gas (see e.g. col 8, line 19-34) and wash solutions (see e.g. col 17, line 25).

Petersen does not establish how the cell suspension is prepared nor how the sample and lysis buffer are introduced.

Nochumson et al teach methods of purification of biomolecules using automated and semi-automated continuous units, which given the broadest interpretation can be considered reactors as the described reactions are undertaken in these units. As demonstrated in figure 2 and

described in ¶ 0041, the cell suspension is loaded and undergoes alkaline lysis following which neutralization occurs. Following this, the lysate is clarified from precipitated cellular debris and impurities (RNA, chromosomal DNA, endotoxin, denatured plasmid). In these steps, the DNA flows through while the impurities remain in the column. The method is performed on a continuous, flow-through device (see e.g. 0019) in which resuspended cells, lysis solution and neutralization solutions are mixed using continuous flow, in line. Nochumson et al teach that lysis solution and cells can either be combined without further mixing prior to entering the lysis reactor (see e.g.0055) or else can be introduced into the lysis reactor and combined for example by use of an impeller mixer (see e.g. ¶ 0036). In the case that the two are part of two independent flows that are mixed in the lysis reactor, one of skill in the art would recognize that these flows would reasonable make a single flow to an inline static mixer by use of a T or Y shaped connector these being configurations that would lead to a single flow (see e.g. ¶ 0055 and figure 1). Effluent from the lysis reaction was directed to neutralization which Nochumson et al teaches occurs by flowing lysate and neutralization solution through an inline state mixer in a continuous mode wherein a continuous flow indicates that flow is constant (see e.g. ¶ 0080). Up to kilograms are purified from about 2kg of wet cell paste (see abstract and ¶ 0054).

The lysate is clarified and this is said to occur by a variety of techniques known to those of skill in the art (see e.g. ¶ 0072-0073 and 0063). This occurs through fluid connections between the units (see e.g. ¶ 0019-0021 and 0054). As well pumps are used to distribute the lysate and mixtures throughout the method. Claim 24 recites that the cells at step a) are cryo- pelleted. It is understood that this intends that the cells prior to use are cryo-pelleted. Nochumson et al teach that the cells can be frozen prior to use in the lysis reaction (see e.g. ¶ 0078) and in the broadest

interpretation, these can be cryo-pelleted cells. Nochumson teaches that clarification occurs for example following alkaline lysis and neutralization by separation of the precipitated impurities by subsequent chromatographic steps (see e.g. ¶ 0048). The chromatographic step uses reactors comprising particulate material. Several wash steps are included as is clarification and concentration (see e.g. ¶ 0050-0053).

As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Exparte Smith --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In this case, both Petersen and Nochumson et al teach methods of isolating biomolecules using automated systems. While Petersen does not include the methods that are set forth in Nochumson, it is clear that the methods of preparing the cell samples as well as introducing lysis buffer and sample into a reactor are well known and available in the art as seen in Nochumson et al. One would have been motivated to do so in order as the ability to modify isolation methods by applying conventional methodologies was well known in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Amendment

Applicants argue that Nochumson does not cure the deficiencies of Petersen et al in that it does not disclose homogenously mixing of the cell suspension and lysis solution when flowing through filling elements in the lysis reactor. However, it is noted that as regards this step the claim recites "introducing a flow of the cell suspension and a flow of a lysis solution into the

lysis reactor into the lysis reactor, the lysis reactor containing filling elements made of glass, plastic, stainless steel or fibrous material, such that the flow of the cell suspension and the flow of the lysis solution into and through the lysis reactor provides homogenous mixing of the flows in the absence of shear forces and whereby the cultivated host cells are substantially disintegrated by alkaline lysis to produce a lysed cell solution." Based upon applicants arguments it appears that the beads are intended to produce the homogenous mixing wherein the flow is around and through the beads. However, as recited, the claims only require that beads be present and that two flows introduced into the lysis reactor provides homogenous mixing. To this end and allowing the full breadth of the claims to be considered, Peterson et al does teach such a limitation.

> In operation, a fluid sample containing a desired analyte. e.g. nucleic acid, is added to the sample port 103 of the cartridge 101 and forced to flow continuously (such as with an electrolytic or mechanical pump) down a channel 105 and into the mixing chamber 107. Lysing reagents are simultaneously released from the storage chamber 109 and forced to flow down a channel 111 and into the chamber 107.

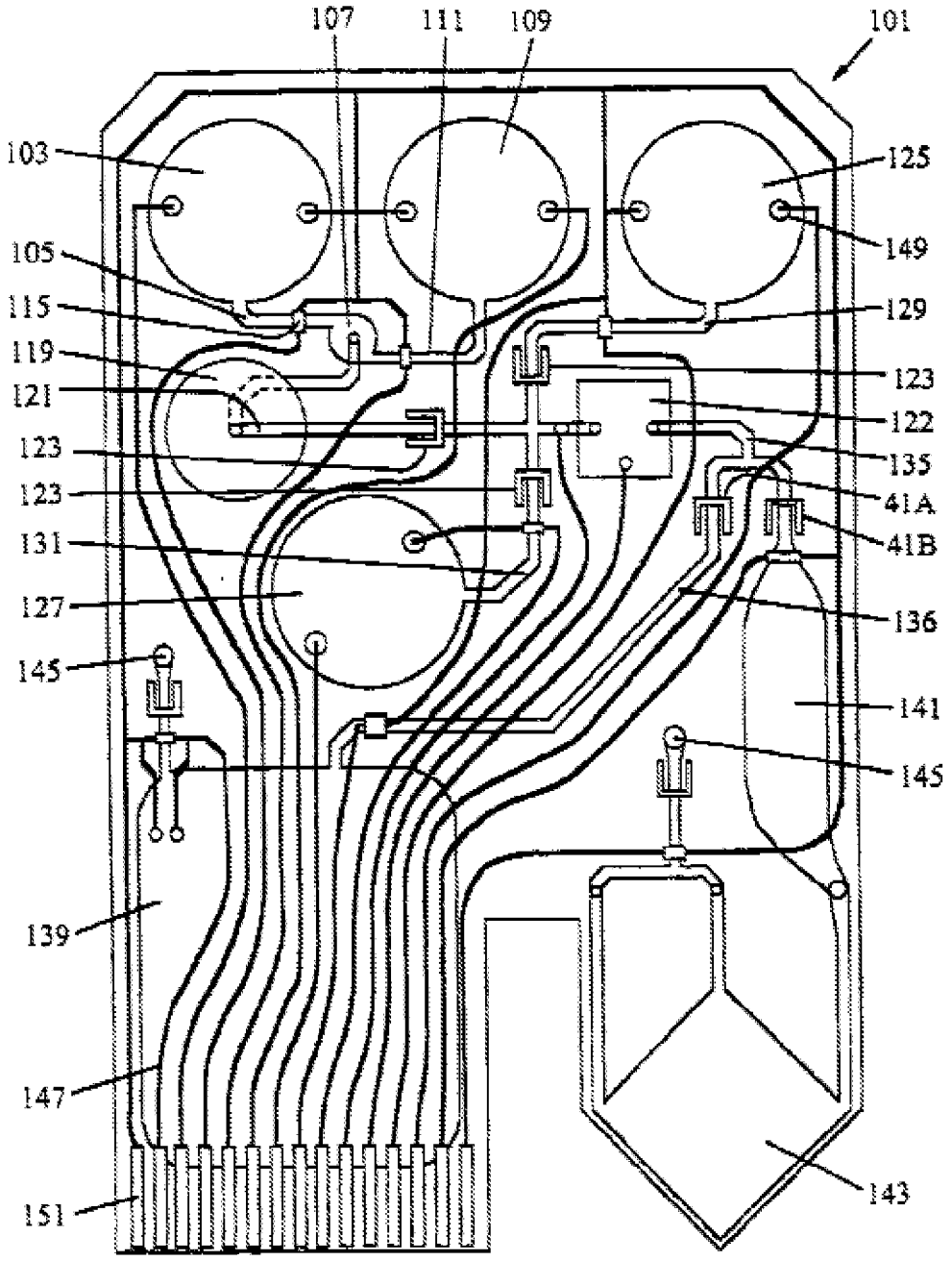
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FIG. 2

The text, in light of the figure above, teaches that lysis solution and cell suspension solution are mixed at a controlled rate into the same chamber. This should absent evidence to the contrary lead to homogenous mixing at required in the claim.

Secondly, all of the instant steps are available in the art and applicable together under the principles of KSR.

> If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. Id. at ,82 USPQ2d at 1396.When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at, 82 USPQ2d at 1396.

Both references teach methods of isolating biomolecules i.e. polynucleotides. Both methods teach use of a lysing reagent for cells. While applicants argue that Petersen does not teach use of cells, the abstract for example teaches a "cartridge may optionally include a lysing region for lysing sample components (e.g., cells, spores, or microorganisms)". As demonstrated above Peterson teaches use of a lysis reagent flow mixed in the lysis reactor with cell suspension for the lysis wherein the cells are lysed. Nochusum also teaches such a step of cellular lysis by alkaline lysis wherein cell solution lysis solution and mixed. Following this both methods teach neutralization and clarification of the biomolecule. Taken together, each of the features of the instant method are demonstrated to be known in the art whereas the improvements of the system taught by Peterson in light of Nochusom et al do not appear to be less than would be predictable by the prior art. It is noted that if applicants can more clearly establish that the homogenization

is due to the beads or that the presence of the beads is not legible than the prior art rejections would not appear to read on the instant claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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